ABC of palliative care
Difficult pain

Lesley Colvin, Karen Forbes, Marie Fallon

Pain occurs in up to 70% of patients with advanced cancer and in about 65% of patients dying from non-malignant disease. In about 10% of these patients the pain is difficult to control. Their pain often falls into one of three categories: it responds poorly to opioids, it is episodic and breaks through despite background opioid analgesia, or it is caused by non-physical factors such as psychosocial distress.

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Pain that responds poorly to opioids

The European Association for Palliative Care guidelines on the use of morphine and alternative opioids in cancer pain confirm oral morphine as the opioid of choice for moderate to severe pain. If the pain is uncontrolled with a dose of morphine that gives the patient intolerable side effects, suggested measures include exploring psychosocial issues, managing the side effects, reducing the dose of opioid, switching to an alternative opioid, or changing the route of administration. The use of adjuvant drugs or co-analgesics may be appropriate. Many such patients will have neuropathic pain.

Patients may be overwhelmed by their situation and the central nervous system can express this as physical pain. Social, psychological, or spiritual factors may be major components of pain

Neuropathic pain

Nociceptive pain results from real or potential tissue damage. Neuropathic pain is caused by damage to the peripheral or central nervous system. Pain may be described as aching, burning, shooting, or stabbing and may be associated with abnormal sensation; normal touch is perceived as painful (allodynia). It may be caused not only by tumour invasion or compression but also by surgery, radiotherapy, and chemotherapy. If neuropathic pain does not respond to opioids, patients will require additional measures.

The early addition of adjuvant analgesics, such as a tricyclic antidepressant or an anticonvulsant, should be considered. The number needed to treat is 3 for both categories. There is no evidence for a specific adjuvant for specific descriptors of neuropathic pain.

In addition, there is no evidence for combining adjuvants. The adjuvant should be chosen for an individual patient based on all symptoms and potential side effects. Doses should be

Classic changes associated with a brachial plexopathy caused by right Pancoast tumour: oedema, trophic changes, muscle wasting

Adjuvant analgesics*

Drug	Dose	Indications	Side effects
Non-steroidal anti-inflammatories (NSAID)—for example, diclofenac	50 mg oral every 8 hours (slow release 75 mg every 12 hours); 100 mg per rectum once a day	Bone metastases, soft tissue infiltration, liver pain, inflammatory pain	Gastric irritation and bleeding, fluid retention, headache; caution in renal impairment
Steroids—for example, dexamethasone	8-16 mg a day; use in morning; titrate down to lowest dose that controls pain	Raised intracranial pressure, nerve compression, soft tissue infiltration, liver pain	Gastric irritation if used with NSAID, fluid retention, confusion, Cushingoid appearance, candidiasis, hyperglycaemia
Gabapentin	100-300 mg nightly (starting dose) (titrate to 600 mg every 8 hours; higher dose may be needed)	Nerve pain of any cause	Mild sedation, tremor, confusion
Amitriptyline (evidence for all tricyclics)	25 mg nightly (starting dose) 10 mg nightly (in elderly patients)	Nerve pain of any cause	Sedation, dizziness, confusion, dry mouth, constipation, urinary retention; avoid in patients with cardiac disease
Carbamazepine (evidence for all anticonvulsants)	100-200 mg nightly (starting dose)	Nerve pain of any cause	Vertigo, sedation, constipation, rash

*Drugs with a primary indication other than pain, but analgesic when used as above.

titrated to balance analgesia with adverse effects. If titration has reached a limit and pain has only partially responded then a second adjuvant may be added in some cases. This usually means a reduction in the dose of the first. A common example of combining adjuvants is gabapentin, which at maximum tolerated dose can sometimes be reduced to allow the addition of amitriptyline.

Non-pharmacological techniques

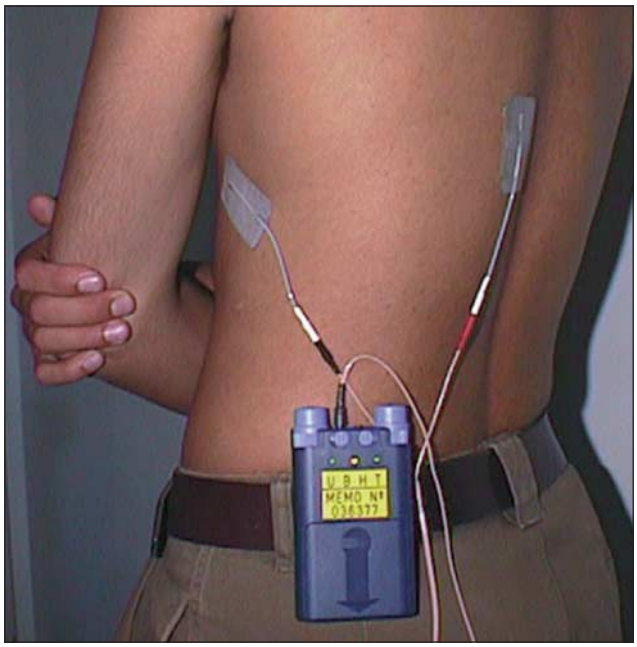
There are several non-pharmacological techniques for the management of neuropathic pain.

Psychological techniques—Psychological techniques, such as cognitive behavioural therapies, include simple relaxation, hypnosis, and biofeedback. These methods focus on overt behaviour and underlying cognitions and train the patient in coping strategies and behavioural techniques. Simple relaxation techniques should also not be forgotten.

Acupuncture has been used successfully in Eastern medicine for centuries. It seems to release endogenous analgesics within the spinal cord. Acupuncture is particularly useful for myofascial pain, which is a common secondary phenomenon in many cancer pain syndromes.

Transcutaneous electrical nerve stimulation (TENS) may have a similar mechanism of action to acupuncture. There is evidence to support its use in both acute and chronic pain.

Herbal medicine and homoeopathy are widely used for pain, but often with little evidence for efficacy. Regulations on safety for these treatments are limited compared with those for conventional drugs, and doctors should be wary of unrecognised side effects.



Transcutaneous electrical stimulation may help patients with neuropathic pain that does not respond to opioids

Episodic pain

The term episodic pain is used to describe any acute transient pain that is severe and has an intensity that flares over baseline. Episodic pain thus encompasses breakthrough pain and incident pain. Breakthrough pain includes pain returning before the next dose of opioid is due or acute exacerbations of pain occurring on the background of pain usually controlled by an opioid regimen. Incident pain is usually defined as that occurring due to a voluntary action, such as movement or passing urine or stool. Pain due to bony metastases exacerbated by movement or weight bearing can be particularly problematic.

Incident pain

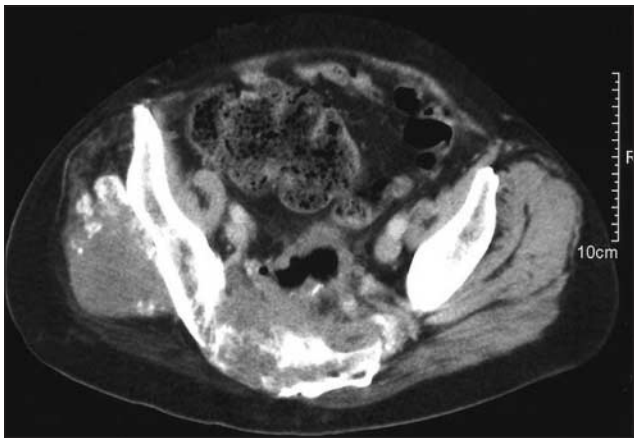
Patients with bony metastases in the spine, pelvis, or femora may have pain that escalates on movement, walking, standing, or even sitting. Opioid analgesics along with non-steroidal anti-inflammatory drugs are the mainstay of treatment, with the aim of making the patient comfortable at rest. Increasing the opioid dose is often unhelpful as a dose sufficient to make movement possible is too sedating when the patient is resting. Rescue or breakthrough doses of normal release opioid are usually used in anticipation of movement, along with non-drug measures such as radiotherapy, possible surgery, and appropriate aids and appliances.

Bisphosphonates are established in the prevention of skeletal events due to metastases from most solid tumours. In some patients, they provide short term analgesia.

Radiographs showing lystic lesions in femur (left) and internal stabilisation of bone (right)

Methadone

Before invasive techniques are considered, it is important to exclude untreated depression, general anxiety, and distress (though untreated pain may also lead to any or all of these).



Computed tomogram of pelvis showing advanced pelvic disease from colorectal tumour resulting in severe pain

It is also worth considering a different drug. Methadone deserves a special mention in this context. It has unusual properties, which we do not fully understand. Its receptor binding profile differs from that of pure μ agonists and it can be remarkably potent at small doses.

Methadone often gives much better analgesia and reduced side effects. In addition, difficult elements of a pain—such as neuropathic or incident pain, or both—may become easier to control.

Starting or switching to methadone can be complicated in some patients, and specialist advice should usually be sought

Invasive analgesic techniques

Despite appropriate use of analgesia and non-drug therapies, chemotherapy, and radiotherapy by multidisciplinary teams, a considerable number of patients will still have uncontrolled pain or unacceptable side effects, or both.

Such patients should be considered for some form of invasive analgesic technique. This may range from a simple nerve block to more invasive techniques such as regional or neurodestructive blocks.

The choice of technique is influenced by:

- Patient's expectations
- Prognosis and required duration of analgesia
- Pathology
- Availability of experts and trained staff.

A basic rule is that the technique with the least likelihood of severe side effects should be chosen. In general, neurodestructive techniques should be reserved for when other measures have failed or when life span is obviously limited.

Spinal routes of drug delivery

With improvements in catheter and pump technology, use of spinal lines is becoming more common in pain control. If the technique is carried out by trained staff, complication rates are low, allowing flexible, long term analgesia that can be used in an outpatient setting. Catheters can be inserted either into the epidural space or into the subarachnoid (intrathecal) space, where the cerebrospinal fluid is found. The line may be tunnelled subcutaneously to reduce risks of infection and movement of the catheter. The choice of technique depends on several factors.

Examples of invasive analgesic techniques

Peripheral	Central
Peripheral nerve block	*Non-destructive*
• Intercostal	• Epidural
• Femoral	• Intrathecal
• Sciatic	
Major nerve block	*Neurosurgical/destructive*
• Brachial plexus	• Rhizotomy
• Psoas	• Cordotomy
• Paravertebral sensory nerve root ablation	• Intrathecal phenol
• Coeliac plexus	

Factors affecting choice of spinal route of delivery

Epidural	Intrathecal
Procedural	
• Simple procedure—local anaesthetic with or without sedation	• Sedation or general anaesthesia usually required
• Fixation can be difficult	• Deep fixation at time of insertion
• Catheters not designed for long term use	• Silastic catheter designed for long term use
• Drug spread may be limited, especially if there is tumour in the epidural space, or scarring related to radiotherapy	• Drug spreads within CSF, unless obstruction to flow; lipid solubility determines degree of spread
• Safety—catheter migration to intrathecal space delivering potential overdose	• Safety—catheter can only migrate out of intrathecal space
Prognosis	
Short term use:	Longer term use:
• Limited prognosis	• Several different options—for example, external or fully implantable
• Other definitive treatment planned—for example, radiotherapy	
• Trial for intrathecal line	

The future

Agents not currently widely available in the UK that may be helpful in managing patients with cancer pain include:

- *Lidocaine patches* are available in the US but limited in the UK. They produce few side effects and studies have shown efficacy in neuropathic pain. We have also used them for bone pain, particularly vertebral metastases, with some success.
- *Pregabalin* has a similar pharmacological profile to gabapentin but is more potent. Randomised controlled trials have shown efficacy against some forms of neuropathic pain and an improved sleep pattern. Titration of dose is easier than with gabapentin.
- *N-methyl-D-aspartate (NMDA) subtype selective agents*—Currently available drugs are non-selective. Animal research suggests particular subtypes of the NMDA receptor may have potential for analgesia with reduced side effects and opioid sparing effects.
- *Calcitonin gene-related peptide (CGRP) antagonists*—CGRP is found in sensory neurones. Non-peptide analogues with a favourable pharmacokinetic profile may have potential as analgesics.

Further reading

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